

US and EU Regulatory Framework

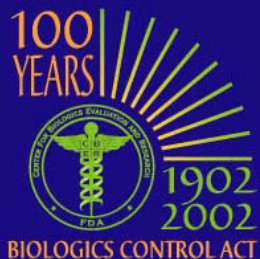
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“Surveillance and Screening of Blood
Borne Pathogens”

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Background for US Tissue Regulations

- Interim final rule, December 1993
 - ◆ first tissue rule; published in response to infectious disease concerns
- Final rule, July 1997
- Legal Authority: Section 361 of Public Health Service (PHS) Act - prevention of communicable disease transmission--no premarket approval required

Background for US Tissue Regulations

- Proposed Approach to Regulation of Human Cells and Tissues – February 1997 [62 FR 9721—March 1997]
 - ◆ New paradigm for regulation
 - ◆ Least burdensome regulation
 - ◆ Tiered risk based approach
 - ◆ Broad scope of cells and tissues
 - ◆ Implemented through rulemaking
- Led to the current round of rulemaking – summarized following slides

Overview of US Tissue-related regulations currently in place

Regulation Subparts	Proposed	Final	Effective Date
Establishment Registration and Product Listing	1998	2001	2001 for establishments regulated under 1270 2004 for newly regulated establishments
Donor Eligibility	1999	2004	May 25, 2005
Current Good Tissue Practices (GTP): Inspection and Enforcement	2001	2004	May 25, 2005

Guidances for the Regulations

- Draft – Preventive Measures to Reduce the Possible Risk of Transmission of CJD/vCJD by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - June 2002
- Draft – Eligibility Determination for Donors of HCT/Ps - May 2004
- Final - donor eligibility guidance will combine the above drafts – FDA is addressing comments to the docket
- Good Tissue Practices guidance – currently leveraging with industry professional associations to develop draft guidance
- <http://www.fda.gov/cber/tissue/docs.htm>

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004

- Directive sets minimum standards for tissues and cells; Compliance date for adopting the directive is 7 April 2006
- Applies to tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone-marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells and adult and embryonic stem cells
- Does not apply to autologous grafts, blood and blood products, organs

Directive 2004/23/EC

- Scope of document – applies to donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (and related manufactured products) intended for human applications
- Has articles related to accreditation, inspections, traceability, import and export, registration of establishments, notification of adverse events, procurement, various management issues, processing, storage conditions, distribution, labelling, documentation and packaging (among others)

Directive 2004/23/EC

- Certain technical implementing measures are contained in Article 28 and those are under development through a committee process (legislative procedure known as Comitology); not yet completed
- “Selection criteria for the donor of tissues and/or cells” as well as “laboratory tests required for donors” are included in Article 28

How FDA defines tissues for transplantation

- Human cells, tissues, or cellular or tissue-based products (HCT/Ps) are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient
- An HCT/P is NOT an organ – vascularized organs (e.g., liver, kidney, heart) are regulated within the Department of Health and Human Services by Health Resources and Services Administration
- 21 Code of Federal Regulations 1271.3(d)

Examples of HCT/Ps

■ Currently regulated tissues

- Bone
- Tendon
- Corneas
- Skin
- Ligament
- Other cells and tissues that require IND

■ “Newly” regulated tissues after 5/25/05

- Reproductive Tissues
- Hematopoietic stem/progenitor cells from peripheral blood and from umbilical cord blood
- Heart Valve allografts
- Dura Mater

Donor Eligibility and RCDADs

- Donor Eligibility rule defines relevant communicable disease agents or diseases (RCDADs); establishments must screen and/or test for RCDADs
- Defined in 1271.3(r) – (1) lists particular RCDADs and (2) describes when communicable disease agents or diseases may be added to the list of RCDADs – in order to allow additions based on emerging infectious diseases
- Additions to the “list” of RCDADs would be added through guidance (draft, public comment, then finalize, except in cases of public health emergency)

RCDADs

- For all HCT/Ps
 - ◆ HIV, types 1 and 2
 - ◆ HBV
 - ◆ HCV
 - ◆ Human TSE, including CJD
 - ◆ Treponema pallidum (agent of syphilis)
- For viable, leukocyte-rich HCT/Ps
 - ◆ HTLV, types I and II
- For reproductive HCT/Ps
 - ◆ Chlamydia trachomatis
 - ◆ Neisseria gonorrhea

Additional RCDADs

- The donor eligibility draft guidance adds new RCDADs according to definition in § 1271.3(r)(2) (published May 2004; not finalized)
- “FDA believes that the following meet the standards for identification of relevant communicable disease agent”—
 - ◆ West Nile Virus
 - ◆ Sepsis
 - ◆ Vaccinia (Smallpox vaccination)
 - ◆ Severe Acute Respiratory Syndrome (SARS)

Donor Testing

- Interpretation of test results
 - ◆ Only according to manufacturer's instructions in the PI
- Specimen collection should be at same time as, or within 7 days before or after, collection of the cells or tissues with certain exceptions
- Donors who have had transfusions or infusions 48 hours prior to specimen collection should be evaluated for plasma dilution or excluded (algorithm included in guidance)

Donor Testing

- Specifically recommended tests include FDA licensed (or cleared) screening tests for
 - ◆ HIV types 1 and 2 – anti-HIV-1 *and* anti-HIV-2 or licensed combination test
 - ◆ HBV – HBsAg *and* anti-HBcore (total=IgG+IgM)
 - ◆ HCV – anti-HCV
 - ◆ *Treponema pallidum* serological test for syphilis (Donor with reactive non-Treponemal screening test and nonreactive specific Treponemal confirmatory test is permitted to donate)

Donor Testing

- Additional screening tests for viable, leukocyte-rich cells or tissue
 - ◆ HTLV types I and II – FDA-licensed anti-HTLV I/II
 - ◆ CMV – not RCDAD, but must test, using FDA-cleared screening test for anti-CMV.
- Additional tests for genitourinary diseases for donors of reproductive cells and tissues
 - ◆ *Chlamydia trachomatis*
 - ◆ *Neisseria gonorrhea*
 - ◆ Currently no FDA-licensed, approved, or cleared donor *screening* tests for either.

NAT and Donor Testing

- DE Draft Guidance published before any NATs were approved for use in cadaveric specimens; at that time only HIV and HCV were licensed for use in blood donor (or other living donors) screening
- Draft guidance states “As more information becomes available, FDA may recommend these tests for use in cadaveric tissue donors.”
- “FDA does recommend that living donors of HCT/Ps (e.g., hematopoietic stem/progenitor cell donors, semen donors) be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV.”

Currently Licensed NAT test kits for donor screening

- Gen-Probe/Chiron – Procleix HIV-1/HCV Nucleic Acid Test (TMA) [B, P, L/O, C]
- National Genetics Institute – UltraQual HIV-1 RT-PCR & HCV RT-PCR Assays [P]
- Roche Molecular Systems – COBAS AmpliScreen HIV-1 & HCV Assays (PCR) [B, P, L/O, C]; HBV Assay (PCR) [B, P]
- B – Blood P – Plasma L/O - Living and Organ donors C - Cadaveric

NAT Donor Screening in the Pipeline*

- WNV – under IND: Gen-Probe [B, P, L/O, C]; Roche Molecular Systems [B, P]
- HBV – Gen-Probe has HBV as part of multiplex test under consideration for BLA at this time [B, P, L/O, C]; RMS has HBV NAT cadaveric indication under consideration for BLA at this time

* Publicly available information, with knowledge of manufacturer

Cadaveric claims for infectious disease screening test kits

- Claims may be obtained as an additional claim (or supplement on already approved test kits) for test kits with an indication for use in screening blood donors
- Guidance published November 2004
“Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” [not NAT-specific]
- Least burdensome approach

Minimal study requirements for cadaveric indication

- Studies – sensitivity, specificity, reproducibility
- May do studies of matched pairs of pre- and post-mortem specimens OR spiking studies (approach we have seen) using spiked cadaveric specimens + spiked unmatched pre-mortem specimens
- Minimum of 50 specimens for sensitivity and specificity studies; 20 specimens for reproducibility

Minimal study requirements for cadaveric indication

- Minimum of 3 test kit lots for each study
- Plasma dilution must be taken into consideration
- Additional information about donors of the cadaveric specimens:
 - ◆ Time between death and specimen collection; how/where specimen was collected
 - ◆ Use hemolyzed specimens, note degree of hemolysis
 - ◆ Note information about storage and handling conditions of the specimens

Cadaveric Indication

- Notable issues with HCT/P specimens
 - ◆ No validation of testing after long term specimen storage (this would be very helpful to the HCT/P industry)
 - ◆ Claims for HCT/P donors may only use individual donor testing and may not be pooled testing unless separate validation is performed (none to date)
 - ◆ Turnaround time is often an issue with cadaveric HCT/Ps – corneas are released in <7 days
 - ◆ It is helpful to have claims for both serum and plasma for cadaveric donors because of limited specimen volume

Further Information

- Cadaveric guidance located at <http://www.fda.gov/cber/gdlns/cadbldhctp.pdf>
- Cadaveric claims are jointly reviewed by OCTGT and OBRR
- Licensed/Approved HIV, HTLV and Hepatitis Tests
<http://www.fda.gov/cber/products/testkits.htm>
- All tissue related publications can be found at <http://www.fda.gov/cber/tissue/docs.htm>
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